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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,044	04/07/2006	Anne Angelillo-Scherrer	50304/009003	1775

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EXAMINER	
DEBERRY, REGINA M	
ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
05/22/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/595,044	ANGELILLO-SCHERRER ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21 and 28-32* is/are pending in the application.

4a) Of the above claim(s) *28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 30-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment and Applicant's arguments, filed 10 February 2009, have been entered in full. Claims 28 and 29 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1-20, 22-27 are canceled. New claims 31 and 32 are added. Claim 21 was amended.

Claims 21, 30-32 are under examination.

Withdrawn Objections And/Or Rejections

The rejection to claim 26 under 35 U.S.C. 112, second paragraph, as set forth at pages 2-3 of the previous Office Action (12 September 2008), is *withdrawn* in view of the amendment (10 February 2009).

The rejection to claims 21-27 and 30 under 35 U.S.C. 112, first paragraph, enablement, as set forth at pages 3-8 of the previous Office Action (12 September 2008), is *withdrawn* in view of the amendment, Applicant's arguments regarding the specification's teaching of reticulocyte indexes (indicative of erythropoiesis, page 28, lines 19-21) and Applicant's submission of Exhibit 1 (Angelillo-Scherrer et al.; J. Clin. Invest.) which teach Gas6-/- knockout mice as an animal model for anemia (10 February 2009).

The objection to claim 21, as set forth at page 10 of the previous Office Action (12 September 2008), is *withdrawn* in view of the amendment (10 February 2009).

Claim Rejections-35 USC § 112, First Paragraph, Written Description

Claims 21, 30-32 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The basis for this rejection is set forth at pages 9-10 of the previous Office Action (12 September 2008).

Applicant argues that that claim 21 has been amended to recite particular Gas6 compounds and erythropoietin proteins described in the specification as filed. Applicant argues that in view of the teachings of the specification, one skilled in the art would recognize that Applicants were in possession of the glycosylation variants, point mutations, and deletion mutants of erythropoietin (EPO) and Gas6 encompassed by claim 21, as amended, and its dependent claims at the time of filing.

Applicant's arguments have been fully considered but are not found persuasive. The Examiner's explanation is based on the discussion from Examples 7-11 of the revision to the Written Description Training Materials (March 25, 2008). Claim 21 does not recite particular Gas6 compounds and erythropoietin proteins. Claim 21 is a genus claim. The claim encompasses one or more amino acid substitutions, deletions, insertions and/or additions made to Gas6 and EPO. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to Gas6 and EPO. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification does not describe any members of the claimed genus by complete structure. No common structural attributes identify the members of the substitution,

deletion and insertion variant genus. There is no information about which amino acids can vary in Gas6 and EPO and still retain a synergistic rescue effect on erythropoiesis. No correlation between this function and the protein's structure is disclosed (e.g., by identifying which amino acids are involved in the active site, substrate binding, etc.). Conservation of structure is not necessarily a surrogate for conservation of function. In this case, there is no disclosed correlation between structure and function. Those of skill in the art might require more or less correlating information depending on the kind of protein activity. If activity X is simply structural, e.g., a member of the collagen class, correlating information might not be a critical factor. However, if activity X is as a ligand (i.e. Gas6 and EPO), and there is no disclosure of the domain(s) responsible for the ligand activity (thus resulting in a synergistic rescue effect on erythropoiesis), the absence of information may be persuasive that those of skill in the art would not take the disclosure as generic. Accordingly, one of skill in the art would not accept the disclosure of Gas6 and EPO as representative of other proteins having the claimed activity. Because the disclosure fails to describe the common attributes or characteristics that identify substitution, deletion and insertion variant members of the genus, and because the genus is highly variant, Gas6 and EPO is insufficient to describe the genus.

Lastly, the instant specification provides written description for a physiologically tolerated salt of wildtype Gas6 (page 11, line 24-page 12, line 13), but not for a physiologically tolerated salt of EPO. The disclosure fails to describe the common attributes or characteristics of physiologically tolerated salts of EPO.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

NEW CLAIM REJECTIONS/OBJECTIONS

Claim Rejections-35 USC § 112, First Paragraph, Written Description (New Matter)

Claims 21, 30-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The specification as originally filed does not provide support for the invention as now claimed:

"..a point mutant or deletion mutant of erythropoietin which retains stimulation of the production of red blood cells.." (claim 21).

Applicant's amendment, filed 10 February 2009, asserts that no new matter has been added and directs support to page 12 for the written description for the above-mentioned "limitations". The Examiner cannot locate the wording or connotation of the instant claims.

The specification as filed does not provide a written description or set forth the metes and bounds of this "limitations". The instant claims now recite limitations which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as-filed. Applicant is required to cancel the new matter in the

response to this Office action. Alternatively, Applicant is invited to provide specific written support for the "limitations" indicated above or rely upon the limitations set forth in the specification as filed.

Claim Rejections-35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21, 30-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for the treatment of anemia in a patient which comprises administering to said patient a combination of **wildtype Gas6 protein (or a physiologically tolerated salt of wildtype Gas6 protein)** and **wildtype erythropoietin (or Epoetin or Darbepoietin),** either simultaneously or sequentially, thereby ensuring a synergistic rescue effect on erythropoiesis in said patient,

does not reasonably provide enablement for the claims as currently claimed.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant argues that claim 21 has been amended to recite particular glycosylation variants, point mutations and deletion mutants of Gas6 or EPO which, as taught in the sections of the specification cited above, were known in the art at the time

of filing. Applicant argues that the specification provides the necessary functional criteria (stimulating the production red blood cells) to assess whether or not a given variant/mutation of EPO is encompasses by the present claims. Applicant argues that the specification describes that Gas6 function can be determined by binding to one of its receptors, Axl, Sky and Mer. Applicant cites references WO 2005/007183 and US Patent Application 2003/0077753.

Applicant's arguments have been fully considered but are not deemed persuasive. The instant claims are not drawn to ***specific*** glycosylation variants, point mutations and deletion mutants of Gas6 or EPO and the specification fails to teach how to make any analogue, mutant, variant or derivative of Gas6 protein or EPO protein that results in synergistic rescue effect on erythropoiesis. The instant examples ***only*** employ recombinant wildtype EPO protein and recombinant wildtype Gas6 protein to demonstrate a synergistic rescue effect on erythropoiesis in mice animal models. The reference cited by Applicant (Angelillo-Scherrer et al.; J. Clin. Invest. Feb; 118(2):583-96, 20008) employs recombinant wildtype EPO protein and recombinant wildtype Gas6 protein to demonstrate a synergistic rescue effect on erythropoiesis in mice animal models. Tischer; US Patent Application 2003/0077753 (cited by Applicant) teaches ***specific*** glycosylation variants of EPO. Tischer teaches that mutations were made at specific amino acid residues. Angelillo-Scherrer et al. WO 2005/007183 (cited by Applicant) employs recombinant wildtype EPO protein and recombinant wildtype Gas6 protein to demonstrate a synergistic rescue effect on erythropoiesis in mice animal models. There are no working examples in the specification or in the art, which teach

Gas6 and EPO polypeptides less than 100% identity and that have a synergistic effect on erythropoiesis. The specification fails to teach the A or D domain of Gas6. The specification fails to teach (i) which portion of Gas6 protein is critical to and (ii) what modifications (e.g., substitutions, deletions or additions) one can make to Gas6 will result in protein mutants with the same functions as the Gas6 wildtype protein. A naturally occurring erythropoietin encompasses alternate forms of the gene occupying the same chromosome. The specification fails to teach how to make a naturally occurring erythropoietin. The nature of alleles is that they are variant structures, and in the present state of the art, the structure of one allele does not provide guidance to the existence or structure of other alleles. The specification does not place any limit on the number of nucleotides substitutions, deletions, insertions and/or additions that may be made to Gas6 or EPO. The specification does not provide any guidance as to what changes should be made and which regions of the Gas6 protein and EPO protein that are functionally and structurally critical for a synergistic rescue effect on erythropoiesis. There is no description of variants of Gas6 and EPO that exist, while still maintaining the claimed function. The Examiner cited references to show that the state of the art is such that the relationship between sequence of a protein and its activity is not well understood and is not predictable. Excising out portions of a protein or modifications to a protein, e.g., by substitutions or deletions, would often result in deleterious effects to the overall activity and effectiveness of the protein. Applicant's argument regarding functional assays that can be employed to discern EPO or Gas6 activity is not found persuasive. Even if assays were provided, the specification would not support claims to

EPO or Gas6 polypeptides modified to an unlimited extent relative to those exemplified. The disclosure fails to enable such a myriad of the claimed molecules that not only vary substantially in length (as the instant claims read on fragments) but also in polypeptide composition and to provide any guidance to those skilled generally on how to make and use the claimed genus of polypeptide molecules. It would require an indeterminate quantity of fundamentally unpredictable investigational experimentation of the skilled artisan to generate the infinite number of derivatives encompassed by EPO or Gas6 analogues, mutants, variants or derivatives thereof and screen same for activity. It is in no way predictable that randomly selected mutations, deletions, *etc.* in the disclosed sequence would afford a protein having activity comparable to the one disclosed.

Due to the large quantity of experimentation necessary to generate the infinite number of Gas6 and EPO derivatives recited in the claims and screen same for synergistic erythropoiesis rescue, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 30-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 is indefinite because it recites an improper Markush group. The instant claim recites both “or” and “and”.

Claim 21 is indefinite because of the recitation, "..wherein said erythropoietin is selected from the group consisting of:...a glycosylation variant of erythropoietin, a point mutant or deletion mutant of erythropoietin which retains stimulation of the production of red blood cells and..glycosylation variant, point mutant or deletion mutant..". The limitations “glycosylation variant”, “point mutant” and “deletion mutant” of EPO are repeated twice. It is unclear if the 1st set of mutations in EPO retains the ability to stimulate the production of red blood cells, but the 2nd set of mutation in EPO does not. Clarification is requested.

Claim 21 is indefinite because of the recitation, "..a Gas6 mutant having at least 95% sequence at the amino acid level said Gas6 fragment..". It is unclear if the instant claim is suppose to recited, “..at the amino acid level **of** said Gas6 fragment..”. Secondly, it is unclear ***which Gas6 fragment*** (lacking the A domain) or (consisting essentially of the D domain) the claim is referencing? Lastly, the claim is indefinite because of the recitation of sequence percent identity at the amino acid level in the absence of a referenced SEQ ID NO: The metes and bounds of claim cannot be determined.

Objections

Claim 21 is objected to because "erythropoietin" is misspelled.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
Primary Examiner, Art Unit 1647

/R. M. D./
Examiner, Art Unit 1647
5/18/09